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Patients with Axial Spondyloarthritis fulfilling imaging arm of ASAS classification criteria: Baseline Clinical Characteristics and Subset Differences in a Single Centre Cohort

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Abstract

Objective: This study compared demographic, clinical and laboratory characteristics between patients with radiographic and non-radiographic axSpA.

Methods: A total of 246 patients with axSpA fulfilling the imaging arm of ASAS classification criteria were recruited to the study. A total of 140 patients were diagnosed as nr-axSpA, and 106 patients had AS. Sociodemographic characteristics, disease manifestations, clinical and laboratory disease activity were analysed.

Results: More nr-axSpA patients were females (61.4%) compared to 24.7% of AS patients. First symptoms developed earlier in AS patients compared to nr-axSpA (23.0 (IQR 17.5-30.0) vs. 27.8 (IQR 21.0-33.7) years, p=0.001). Positive family history in first-degree relatives was more frequent in nr-axSpA compared to AS patients (44.3% vs. 22.6%, p<0.001). Disease manifestations did not differ, but patients with nr-axSpA experienced peripheral arthritis more frequently (35.7% vs. 17.0%, p=0.001) with less hip involvement (8.6% vs. 18.9%, p=0.022) compared to patients with AS. Patients with AS exhibited worse spinal mobility, physical function compared to nr-axSpA. Ankylosing Spondylitis Disease Activity Scores and CRP levels were significantly higher in patients with AS compared to nr-axSpA (2.4 (IQR 1.7-2.8) vs. 2.0 (IQR 1.1-2.3), p=0.022 and 7.1 (IQR 2.6-14.9) vs. 2.5 (IQR 0.8-8.2) mg/L, p<0.001, respectively).

Conclusions: Our data demonstrated some known and also novel differences between the two imaging arm fulfilling axSpA subgroups. Non-radiographic patients had a greater frequency of positive family history contrary to previous findings, they experienced shorter disease duration, milder disease activity and better functional status with less hip involvement but more peripheral arthritis compared to patients with AS.

Strengths and limitations of this study:

- A strength of this study is the large sample size.
- This is the first study investigating the differences between AxSpA patients in Czech Republic.
- We included only patients fulfilling radiographic arm of ASAS classification criteria (AS and nr-axSpA), patients fulfilling clinical arm were excluded.
- MRI was performed in several imaging centres.

Key words: Spondyloarthritis, non-radiographic axial spondyloarthritis, ankylosing spondylitis, disease activity

Introduction:

Spondyloarthritis (SpA) is a frequent chronic inflammatory disease that primarily affects the axial skeleton and causes a typical lower back pain. SpA is a heterogeneous group of disorders that share common clinical features, including peripheral arthritis, enthesitis and extraarticular manifestations, such as uveitis, inflammatory bowel disease or psoriasis [1]. SpA is divided into predominantly axial or predominantly peripheral disease based on the sites of inflammation [2]. Ankylosing spondylitis (AS) is a prototype of axial spondyloarthritis (axSpA). The prevalence of axSpA is approximately 0.7-1.4% in the general population [3]. Patients generally develop signs of inflammatory back pain that correspond to sacroiliitis (or spondylitis) as detected by imaging. AS is a slowly progressive disease that is defined using modified New York classification criteria, in which conventional radiographs of the sacroiliac joints exhibit definite structural changes [4].

Many patients develop similar axial symptoms but lack the typical changes on radiographs, which potentially causes delayed or missed diagnosis [5]. Magnetic resonance imaging (MRI) is used to visualise the radiographic changes that typically occur several years after sacroiliac joint inflammation. MRI is also included in the new Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axSpA to enable the diagnosis of non-radiographic axSpA (nr-axSpA) [6]. Nr-axSpA may be a pre-stage of AS, however not all of these patients develop the destructive joint changes that are typical of long-standing disease. Only approximately 10-20% of patients with nr-axSpA develop structural changes and AS over in the subsequent two years, and approximately half of the patients exhibit radiographic sacroiliitis after five years of the disease [7].

Some recent studies investigated differences between these two subgroups [8-10]. These studies varied in male-to-female ratios, the proportion of patients with objective signs of inflammation (such as bone marrow oedema), and the proportion of patients with increased levels of C-reactive protein (CRP), all of which are higher in patients with AS [8-10]. Clinical characteristics such as disease activity, physical impairment and quality of life were comparable between these two subgroups [11, 12]. However, some inconsistencies exist. Therefore, our study described the baseline demographic, clinical, and laboratory characteristics of axSpA patients and examined differences between AS and nr-axSpA subgroups fulfilling the imaging arm of ASAS classification criteria.

Patients and methods

This study is a descriptive, single-centre, cross–sectional, ongoing study of the Prague Spondyloarthritis Cohort (PRASPAC), which included 246 patients who fulfilled the ASAS classification criteria for axSpA [13]. Patients with a suspicion of SpA were referred to our specialised early-SpA centre in the out-patient department of the Institute of Rheumatology mostly by general practitioners/ophthalmologists/rheumatologists (minority of patients by other specialists) from the central region of the Czech Republic. Patients were further classified as AS or nr-axSpA based on radiographic findings, and irrespective of the presence of psoriasis or inflammatory bowel disease (IBD). Patients were classified as nr-axSpA if radiographic changes in the sacroiliac (SI) joints of at least grade II bilaterally or grade III or IV unilaterally were lacking, and positive MRI (i.e., characteristic bone marrow oedema) was present with at least one SpA feature. Patients were classified as AS according to New York classification criteria [4]. Patients who fulfilled only clinical arm of ASAS classification criteria were included in the PRASPAC and underwent the same examination protocol. However, these patients were not included in our analyses. No restrictions for disease duration or treatment protocol were used at inclusion. The study was initiated before anti-TNF treatment was approved for nr-axSpA by local authorities.

All patients were recruited from October 2012 to March 2016 at the outpatient rheumatology department of the Institute of Rheumatology in Prague and were followed every 6 months for the first 2 years. Trained rheumatologists obtained data related to the disease status according to recommended standardised methodologies: metrology (modified Schober, fleche, chin-chest distance, chest expansion), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) [14], swollen and tender joint count (SJC and TJC), physician global assessment (MDGAS), Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP) [15], Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [16], and Bath Ankylosing Spondylitis Functional Index (BASFI) [17]. Laboratory parameters (CRP and erythrocyte sedimentation rate [ESR]) were analysed from blood samples at each visit. Additional data related to the diagnosis were obtained at the recruitment visit, including age at the onset of first symptoms, type of first symptom (e.g., back pain, peripheral arthritis, extraarticular manifestations), age at diagnosis, family history (AS, IBD, psoriasis), inflammatory back pain, occurrence of peripheral or hip arthritis and extraarticular manifestations, previous and current medications (non-steroidal anti-inflammatory drugs [NSAIDs], conventional synthetic disease-modifying anti-rheumatic drugs [csDMARDs], glucocorticoids, biological treatment

[bDMARDs]), HLA-B27 positivity and socio-demographic data (age, gender, body mass index [BMI], current/ex/non-smoker). The local ethics committee of the Institute of Rheumatology in Prague approved this study. Written informed consent was obtained from all patients prior to study initiation. Data presented in this study were collected from the recruitment visit.

Imaging

Radiographs of the SI joints and lumbar and cervical spine from all patients were obtained prior to recruitment, and a trained rheumatologist and/or central radiologist scored the radiographs for the initial disease classification. Radiographic sacroiliitis was scored from grade 0 (normal) to grade 4 (ankylosis) according to the Bennett scoring system [18]. Cervical and lumbar spines were scored according to the modified Stoke AS Spine Score (mSASSS) [19]. A trained rheumatologist scored MRI images from nr-axSpA patients obtained at recruitment. The modified Berlin and the Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system for active changes and modified Berlin scoring system for chronic changes were used [20].

Laboratory analysis

Fasting blood samples were collected from all patients on the same day as the clinical examination. CRP levels were measured using turbidimetry (Beckman Coulter, California, USA), and ESR was measured according to the Fahraeus Westergren method in a routine clinical laboratory. HLA-B27 was detected using flow cytometry kits (IOTest HLA-B27-FITC/HLA-B7-PE, Beckman Coulter - Immunotech SAS; Marseille, France) and BDTM HLA-B27 Kit (BD Bioscience; San Jose, CA)) according to the manufacturer's protocol.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 5.1. A Kolmogorov-Smirnov test of normality was performed for all variables. Categorical variables were compared between groups using Fisher's exact test. Data for continuous variables are presented as the median with interquartile range (IQR), and variables were compared using Mann-Whitney tests if not stated otherwise. P values below 0.05 with CI 95% were considered statistically significant for all statistical evaluations.

Results

Demographic data

A total of 246 patients who fulfilled ASAS classification criteria for axSpA were included in this study. Table 1 shows patients' demographic data. The entire group consisted of 106 patients with AS (43.1%) and 140 patients with nr-axSpA (56.9%). There was no gender predominance in the entire group (male-to-female ratio: 53.3% vs. 46.7%). However, most of the nr-axSpA patients were females compared to the AS patients (61.4% vs. 27.4%, p<0.001). There were no significant differences in age, BMI or smoking history between AS and nr-axSpA patients.

Mean age at the diagnosis was 33.2 (27.7-41.6) years, and the disease duration from first symptoms was 7.8 (3.1-14.5) years for the entire axSpA group. The first clinical symptoms developed earlier in patients with AS compared to patients with nr-axSpA (23.0 (17.5-30.0) vs. 27.8 (21.0-33.7) years, p=0.001). AS patients were younger at the time of diagnosis than nr-axSpA patients (32.7 (26.8-39.2) vs. 35.2 (28.8-45.5) years, p=0.023).

Positive family history in first-degree relatives was seen in 35% of axSpA patients, and it was more frequent in nr-axSpA patients compared to AS patients (44.3% vs. 22.6%; p<0.001).

Clinical parameters

Disease activity as determined by ASDAS-CRP was 2.2 (1.4-2.8) in the entire axSpA group, and it was significantly higher in AS patients compared to nr-axSpA patients (2.4 (1.7-2.8) vs. 2.0 (1.1-2.3), p=0.022). The mean BASDAI was 2.6 (1.2-4.7) in the entire axSpA group, but it did not significantly differ between AS and nr-axSpA subgroups. AS patients with AS exhibited significantly worse spinal mobility (chin-chest distance (2.0 (0.0-3.0) vs. 1.0 (0.0-2.0) cm, p=0.008) and modified Schober distance (4.0 (3.0-5.0) vs. 4.5 (3.5-5.5) cm, p<0.001) compare to nr-axSpA patients. AS patients exhibited worse BASFI compared to nr-axSpA patients (1.8 (0.7-3.3) vs. 1.1 (0.3-2.9), p=0.030).

Peripheral arthritis and hip arthritis were present in 27.6% and 13.0% of all axSpA patients, respectively. Patients with nr-axSpA exhibited peripheral arthritis more frequently and hip arthritis less frequently compared to AS patients (35.7% vs. 17.0% and 8.6% vs. 18.9%, p=0.001 and p=0.022, respectively). SJC and TJC were significantly higher in nr-axSpA patients compared to AS patients (mean SJC: 0.5 ±1.5 SD vs. 0.3 ±1.4 SD and mean TJC 0.5 ±1.4 SD vs. 0.3 ±1.7 SD, p=0.021 and p=0.015, respectively). There were no significant

differences in the first symptoms of the disease, extraarticular manifestations, or current and previous medications. Division of axSpA according to gender to compare joint variables (peripheral arthritis, hip arthritis, SJC and TJC) revealed a significant difference only in hip arthritis that was more frequent in male patients compared to female patients (20% vs. 5.3%; p<0.001). Tables 1 and 2 present all clinical parameters.

Laboratory parameters

CRP serum levels (7.1 (2.6-14.9) vs. 2.5 (0.8-8.2) mg/L, p<0.001) and ESR (12.0 (4.4-22.0) vs. 7.0 (3.0-16.0) mm/h, p=0.007) were significantly higher in AS patients than nr-axSpA patients. HLA-B27 was found in most of the patients in this study (87.4%), and the prevalence of HLA-B27 was not significantly higher in AS patients than nr-axSpA patients (92.5% vs. 83.6%, p=0.051). Tables 1 and 2 show all of the laboratory parameters.

Discussion

This study investigated similarities and differences between AS and nr-axSpA subgroups fulfilling the imaging arm of ASAS classification criteria in a single-centre axSpA cohort in Prague.

Demographic characteristics were comparable in both axSpA subgroups, except the male-to-female ratio, which was higher in AS patients than nr-axSpA patients, which is consistent with previous studies [8-11]. The nr-axSpA subgroup consisted of more female patients than the AS subgroup. Our data also demonstrated that nr-axSpA patients presented first symptoms of the disease later than AS patients, which is also consistent with some previous studies [21, 22]. Male gender and early onset of the disease in AS were proposed prognostic factors for severe radiographic damage [23, 24], and female gender was associated with milder disease and later onset [25]. Female predominance and later disease onset in nr-axSpA may underlie the lower percentage of nr-axSpA female patients progressing to AS [11].

Positive family history is a common finding in SpA. For example, siblings of HLA-B27-positive AS patients exhibit a 50x increased risk of developing AS compared to the general population [26]. Many patients, especially HLA-B27-positive patients, have a positive family history of SpA or related diseases. More than one third of all cases had first-degree relatives with AS, psoriasis or IBD in our study, and to our knowledge, we are the first to present that this association was more frequent in the nr-axSpA subgroup than in the AS subgroup. This could be explained by selecting patients fulfilling only imaging arm of ASAS criteria into our study or by the fact that patients with first symptoms and positive family history possibly search doctors examination earlier and more often than those lacking positive family history. Furthermore, recent findings even suggest that a substantial proportion of healthy first-degree relatives of HLA-B27-positive AS patients exhibit clinical and/or imaging abnormalities suggestive of SpA, and almost 33% may be classified as SpA especially as nr-axSpA [27]. Comparison of first degree relatives across gender did not reveal any differences, but a significantly greater frequency of positive family history was previously described in females [28, 29]. This result contrasts one study of the occurrence of SpA in first-degree relatives of patients in which no gender differences were demonstrated [30].

The disease activity of axSpA patients, using ASDAS score and CRP levels, differed between subgroups but remained similar when BASDAI was used in the present study. AS patients exhibited significantly higher disease activity as determined by ASDAS and acute phase reactants compared to nr-axSpA patients, which is consistent with previous studies [11, 31].

Elevated CRP may predict the development of radiographic changes [8]. However, recent findings demonstrated similar disease activity as determined by the BASDAI index between AS and nr-axSpA subgroups [8]. The BASDAI may not be a reliable index for evaluating disease activity in axSpA because it reflects subjective perceptions of the disease. Spinal mobility measures and BASFI reflecting movement functions were significantly worse in the AS patients, which is consistent with the results of the GESPIC cohort [11]. These results are most likely due to advanced structural changes in the spine of AS patients.

A recent meta-analysis found that arthritis and extraarticular manifestations were equally prevalent in AS and nr-axSpA subgroups, except uveitis, which is slightly more prevalent in AS patients [12]. However, our study demonstrated a significant difference between the occurrence of peripheral arthritis, which was more frequent in the nr-axSpA than AS subgroup. A large SpA cohort recently demonstrated more peripheral involvement in females [28], which may explain the higher prevalence of peripheral arthritis in nr-axSpA with the larger female predominance, at least in the present study. Hip involvement was more frequent in AS patients than the nr-axSpA patients in our cohort. Hip involvement is more prevalent in patients with a younger disease onset, which may be associated with more severe axial disease, and it represents a prognostic factor for severe outcome [24, 32].

Our study has some limitations. First, four assessors examined the patients, which may cause possible inter-rater variability. Second, MRI was performed in several centres, and it was not available for re-assessment at the time of data analysis for all cases. Therefore, we followed the written report from the MRI examination to divide the patients into AS or nr-axSpA subgroups. Lastly, we excluded nr-axSpA patients fulfilling only the clinical arm of ASAS classification criteria for significantly lower participation in the study and relatively low sensitivity and specificity of the criteria sometimes causing questionable or borderline diagnosis.

Conclusions:

In summary, we confirmed some of the similarities and differences between AS and nr-axSpA patients fulfilling the imaging arm of ASAS classification criteria but also found some novel aspects. To our knowledge, we are the first to present that patients with nr-axSpA exhibited more frequent positive family history. Furthermore peripheral arthritis, unlike hip joint involvement, was more prevalent in nr-axSpA patients compared to AS patients in our study.

However, patients with nr-axSpA and AS exhibited many similarities despite the issue of classification, which suggests a common therapeutic approach.

Key messages:

1. Non-radiographic axial spondyloarthritis and ankylosing spondylitis have mostly similar profile of disease features.
2. Differences can be found in more frequent development of peripheral arthritis in nr-axSpA contrary to hip arthritis.
3. Patients with nr-axSpA often exhibit positive family history of typical SpA features.
4. We should approach all axSpA patients similarly despite of classification ambiguity.

List of abbreviations:

AS – Ankylosing spondylitis

ASAS - Assessment of SpondyloArthritis International Society

ASDAS - Ankylosing Spondylitis Disease Activity Score

AxSpA – Axial spondyloarthritis

BASDAI - Bath Ankylosing Spondylitis Disease Activity Index

BASFI - Bath Ankylosing Spondylitis Functional Index

BMI - Body mass index

BDMARDs - Biological treatment

CRP – C reactive protein

CsDMARDs - Conventional synthetic disease-modifying anti-rheumatic drugs

ESR – Erythrocyte sedimentation rate

IBD – Inflammatory bowel disease

MASES - Maastricht Ankylosing Spondylitis Enthesitis Score

MDGAS - Physician global assessment

MRI – Magnetic resonance imaging

MSASSS – Modified stoke axial spondyloarthritis spinal score

Nr-axSpA – Non-radiographic axial spondyloarthritis

NSAIDs - Non-steroidal anti-inflammatory drugs

PRASPAC - The Prague Spondyloarthritis Cohort

SD – Standard deviation

SJC – Swollen joint count

SI - Sacroiliitis

SpA - Spondyloarthritis

SPARCC - Spondyloarthritis Research Consortium of Canada

TJC – Tender joint count

Declaration

Ethic approval

The local ethics committee (Mgr. Ivana Půtova) of the Institute of Rheumatology in Prague approved this study. Written informed consent was obtained from all patients prior to study initiation.

Conpeting of interest

All authors declare that they have no competing interests.

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Authors Contribution

MH, KB, LS, KP designed the study. MH, KB, SF, KZ, MG, JH, MF, MT, KP, JS prepared the clinical database or took clinical care of axSpA patients in the PRASPAC cohort. KB, MT, LS did the data analysis. KB, MT and LS drafted the manuscript. KB, JG determined the radiographic and MRI scores. All authors contributed to and approved the final manuscript.

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Tables:

Table 1 Baseline characteristics: demographic and clinical features of spondyloarthritis

Characteristic	SpA	nr-axSpA	AS	M-W/FET p
Age (years), median (IQR)	34.7 (29.3-43.5)	36.9 (29.2-46.9)	36.0 (29.3-44.1)	-
Gender: Males number (%)	131 (53.3)	54 (38.6)	77 (72.6)	**< 0.001**
BMI (kg/m^2), median (IQR)	24.3 (21.7-27.4)	24.8 (21.6-28.2)	24.2 (22.6-26.6)	0.946
History of smoking:				
Ever-smoker, number (%)	107 (43.7)	52 (37.1)	55 (52.4)	0.138
HLA-B27 positive, number (%)	215 (87.4)	117 (83.6)	98 (92.5)	0.051
Disease duration, years (IQR)	7.8 (3.1-14.5)	5.6 (2.6-12.2)	10.2 (5.1-15.5)	**0.001**
First symptom:				0.086
Back pain, number (%)	195 (79.3)	104 (74.3)	91 (85.8)	
Peripheral arthritis, number (%)	27 (11.0)	19 (13.6)	8 (7.5)	
Extraarticular manifestations, number (%)	24 (9.8)	17 (12.1)	7 (6.6)	
Family history:				
First degree relatives, number (%)	86 (35.0)	62 (44.3)	24 (22.6)	**< 0.001**
Second degree relatives, number (%)	28 (11.4)	18 (12.9)	10 (9.4)	0.426
Past history of:				
Peripheral arthritis, number %	68 (27.6)	50 (35.7)	18 (17)	**0.001**
Hip arthritis, number %	32 (13.0)	12 (8.6)	20 (18.9)	**0.022**
Uveitis, number %	63 (25.6)	39 (27.9)	24 (22.6)	0.379
IBD, number %	13 (5.3)	9 (6.4)	4 (3.8)	-
Psoriasis, number %	1 (0.4)	0 (0)	1 (0.9)	-
Other, number %	3 (1.2)	1 (0.7)	2 (1.9)	-
Current symptoms:				
MASES, median (IQR)	0.0 (0.0-2.0)	0.0 (0.0-2.0)	0.0 (0.0-1.3)	0.289
SJC, mean (±SD)	0.4 (1.4)	0.5 (1.5)	0.3 (1.4)	**0.021**
TJC, mead (±SD)	0.4 (1.4)	0.5 (1.4)	0.3 (1.7)	**0.015**
Current medication:				
NSAIDs, number %	126 (51.2)	71 (50.7)	55 (51.9)	-
CsDMARDs, number (%)	39 (15.9)	26 (18.6)	13 (12.3)	-
Corticosteroids, number (%)	5 (2)	2 (1.4)	3 (2.8)	-
BoDMARDs/bsDMARDs, number (%)*	6 (2.4)	2 (1.4)	4 (3.8)	-

AS, ankylosing spondylitis; BMI, body mass index; boDMARDs, biological original disease modifying anti-rheumatic drugs; bsDMARDs, biosimilar disease modifying anti-rheumatic drugs; csDMARDs, conventional synthetic disease modifying anti-rheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; IBD, inflammatory bowel disease; IQR, interquartile range; M-W/FETp, Mann-Whitney/ Fisher exact test p value; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; nr-axSpA, non-radiographic axial spondyloarthritis; SJC, swollen joint count; SpA, spondyloarthritis; TJC, tender joints count; *Adalimumab 2 patients; Certolizumab 1 patient; Golimumab 2 patients; Infliximab 1 patient

Table 2: Baseline characteristics: activity and metrology

Characteristic	SpA	nr-axSpA	AS	M-W/FET p
ASDAS-CRP, median (IQR)	2.2 (1.4-2.8)	2.0 (1.1-2.3)	2.4 (1.7-2.8)	**0.022**
BASDAI, median (IQR)	2.6 (1.2-4.7)	2.7 (1.0-4.9)	2.4 (1.2-3.7)	0.362
CRP mg/l	4.3 (1.2-12.0)	2.5 (0.8-8.2)	7.1 (2.6-14.9)	**< 0.001**
ESR mm/h	8.0 (4.0-17.8)	7.0 (3.0-16.0)	12.0 (4.4-22.0)	**0.007**
BASFI, median (IQR)	1.4 (0.5-2.1)	1.1 (0.3-2.9)	1.8 (0.7-3.3)	**0.030**
Metrology:				
Modified Schober (cm), median (IQR)	4.0 (3.0-5.0)	4.5 (3.5-5.5)	4.0 (3.0-5.0)	**< 0.001**
Fleche (cm), median (IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	**< 0.001**
Chin-chest distance (cm), median (IQR)	1.5 (0.0-3.0)	1.0 (0.0-2.0)	2.0 (0.0-3.0)	**0.008**
Chest expansion (cm), median (IQR)	4.0 (3.0-6.0)	4.0 (3.0-6.0)	3.8 (2.0-6.0)	0.136

AS, ankylosing spondylitis; ASDAS-CRP - Ankylosing Spondylitis Disease Activity Score based on CRP; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; M-W/FETp, Mann-Whitney/ Fisher exact test p value; nr-axSpA, non-radiographic axial spondyloarthritis; SpA, spondyloarthritis

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Cross-sectional study of patients with Axial Spondyloarthritis fulfilling imaging arm of ASAS classification criteria: Baseline Clinical Characteristics and Subset Differences in a Single Centre Cohort

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Cross-sectional study of patients with Axial Spondyloarthritis fulfilling imaging arm of ASAS classification criteria: Baseline Clinical Characteristics and Subset Differences in a Single Centre Cohort

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Abstract

Objective: This study compared demographic, clinical and laboratory characteristics between patients with radiographic and non-radiographic axSpA.

Methods: A total of 246 patients with axSpA fulfilling the imaging arm of ASAS classification criteria were recruited to the study. A total of 140 patients were diagnosed as nr-axSpA, and 106 patients had AS. Sociodemographic characteristics, disease manifestations, clinical and laboratory disease activity were analysed.

Results: More nr-axSpA patients were females (61.4%) compared to 24.7% of AS patients. First symptoms developed earlier in AS patients compared to nr-axSpA (23.0 (IQR 17.5-30.0) vs. 27.8 (IQR 21.0-33.7) years, p=0.001). Disease manifestations did not differ, but patients with nr-axSpA experienced peripheral arthritis more frequently (35.7% vs. 17.0%, p=0.001) with less hip involvement (8.6% vs. 18.9%, p=0.022) compared to patients with AS. Patients with AS exhibited worse spinal mobility, physical function compared to nr-axSpA. Ankylosing Spondylitis Disease Activity Scores and CRP levels were significantly higher in patients with AS compared to nr-axSpA (2.4 (IQR 1.7-2.8) vs. 2.0 (IQR 1.1-2.3), p=0.022 and 7.1 (IQR 2.6-14.9) vs. 2.5 (IQR 0.8-8.2) mg/L, p<0.001, respectively).

Conclusions: Our data demonstrated some known and also novel differences between the two imaging arm fulfilling axSpA subgroups. Non-radiographic patients were mostly women had experienced shorter disease duration, milder disease activity and better functional status with less hip involvement but more peripheral arthritis compared to patients with AS.

Strengths and limitations of this study:

- Strength of this study is the large sample size.

- This is the first study investigating the differences between axSpA patients in the Czech Republic.
- We included only patients fulfilling imaging arm of ASAS classification criteria (AS and nr-axSpA), patients fulfilling only clinical arm were not included.
- MRI was performed in several imaging centres.

Key messages:

1. Non-radiographic axSpA (imaging arm) and ankylosing spondylitis share similar disease manifestations.
2. Non-radiographic axSpA is more prevalent in woman than in man contrary to ankylosing spondylitis.
3. Peripheral arthritis is more frequent and hip arthritis less frequent in non-radiographic axSpA compared to ankylosing spondylitis.
4. All axSpA patients should be approached similarly despite of classification ambiguity.

Key words: Spondyloarthritis, non-radiographic axial spondyloarthritis, ankylosing spondylitis, disease activity

Introduction:

Spondyloarthritis (SpA) is a frequent chronic inflammatory disease that primarily affects the axial skeleton and causes a typical lower back pain. SpA is a heterogeneous group of disorders that share common clinical features, including peripheral arthritis, enthesitis and extraarticular manifestations, such as uveitis, inflammatory bowel disease or psoriasis [1]. SpA is divided into predominantly axial or predominantly peripheral disease based on the sites of inflammation [2]. Ankylosing spondylitis (AS) is a prototype of axial spondyloarthritis (axSpA). The prevalence of axSpA is approximately 0.7-1.4% in the general population [3]. Patients generally develop signs of inflammatory back pain that correspond to sacroiliitis (or spondylitis) as detected by imaging. AS is a slowly progressive disease that is defined using modified New York classification criteria, in which conventional radiographs of the sacroiliac joints exhibit definite structural changes [4].

Many patients develop similar axial symptoms but lack the typical changes on radiographs, which potentially causes delayed or missed diagnosis [5]. Magnetic resonance imaging (MRI) is used to visualise the radiographic changes that typically occur several years after sacroiliac joint inflammation. MRI is also included in the new Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axSpA to enable the diagnosis of non-radiographic axSpA (nr-axSpA) [6]. Nr-axSpA may be a pre-stage of AS, however not all of these patients develop the destructive joint changes that are typical of long-standing disease. Only approximately 10-20% of patients with nr-axSpA develop structural changes and AS over in the subsequent two years, and approximately half of the patients exhibit radiographic sacroiliitis after five years of the disease [7].

Some recent studies investigated differences between these two subgroups [8-10]. These studies varied in male-to-female ratios, the proportion of patients with objective signs of inflammation (such as bone marrow oedema), and the proportion of patients with increased levels of C-reactive protein (CRP), all of which are higher in patients with AS [8-10]. Clinical characteristics such as disease activity, physical impairment and quality of life were comparable between these two subgroups [11, 12]. However, some inconsistencies exist. Therefore, our study described the baseline demographic, clinical, and laboratory characteristics of axSpA patients and examined differences between AS and nr-axSpA subgroups fulfilling the imaging arm of ASAS classification criteria.

Patients and methods

This study is a descriptive, single-centre, cross–sectional, ongoing study of the Prague Spondyloarthritis Cohort (PRASPAC), which included 246 patients who fulfilled the ASAS classification criteria for axSpA [13]. Patients with a suspicion of SpA were referred to our specialised early-SpA centre in the out-patient department of the Institute of Rheumatology mostly by general practitioners/ophthalmologists/rheumatologists (minority of patients by other specialists) from the central region of the Czech Republic. Patients were further classified as AS or nr-axSpA based on radiographic findings, and irrespective of the presence of psoriasis or inflammatory bowel disease (IBD). Patients were classified as nr-axSpA if radiographic changes in the sacroiliac (SI) joints of at least grade II bilaterally or grade III or IV unilaterally were lacking, and positive MRI (i.e., characteristic bone marrow oedema) was present with at least one SpA feature. Patients were classified as AS according to New York classification criteria [4]. Patients who fulfilled only clinical arm of ASAS classification criteria were included in the PRASPAC and underwent the same examination protocol. However, these patients were not included in our analyses. No restrictions for disease duration or treatment protocol were used at inclusion.

All patients were recruited from October 2012 to March 2016 at the outpatient rheumatology department of the Institute of Rheumatology in Prague and were followed every 6 months for the first 2 years. Trained rheumatologists obtained data related to the disease status according to recommended standardised methodologies: metrology (modified Schober, occiput to wall, chin-chest distance, chest expansion), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) [14], swollen and tender joint count (SJC and TJC), physician global assessment (MDGAS), Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP) [15], Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [16], and Bath Ankylosing Spondylitis Functional Index (BASFI) [17]. Laboratory parameters (CRP and erythrocyte sedimentation rate [ESR]) were analysed from blood samples at each visit. Additional data related to the diagnosis were obtained at the recruitment visit, including age at the onset of first symptoms, type of first symptom (e.g., back pain, peripheral arthritis, extraarticular manifestations), age at diagnosis, family history (AS, IBD, psoriasis), inflammatory back pain, occurrence of peripheral or hip arthritis and extraarticular manifestations, previous and current medications (non-steroidal anti-inflammatory drugs [NSAIDs], conventional synthetic disease-modifying anti-rheumatic drugs [csDMARDs], glucocorticoids, biological treatment [bDMARDs]), HLA-B27 positivity and socio-demographic data (age, gender, body mass

index [BMI], current/ex/non-smoker). Both axSpA subsets were treated according to the EULAR recommendations for the management of spondyloarthritis. Patients with mild disease were treated with NSAIDs on demand. Most of the patients with previously developed peripheral arthritis were treated with csDMARDs. Patients with severe disease were treated with bDMARDs. The study was initiated before anti-TNF treatment was approved for nr-axSpA by local authorities. The local ethics committee of the Institute of Rheumatology in Prague approved this study. Written informed consent was obtained from all patients prior to study initiation. Data presented in this study were collected from the recruitment visit.

Imaging

Radiographs of the SI joints and lumbar and cervical spine from all patients were obtained prior to recruitment, and a trained rheumatologist and/or central radiologist scored the radiographs for the initial disease classification. Radiographic sacroiliitis was scored from grade 0 (normal) to grade 4 (ankylosis) according to the Bennett scoring system [18]. Cervical and lumbar spines were scored according to the modified Stoke AS Spine Score (mSASSS) [19]. A trained rheumatologist scored MRI images from nr-axSpA patients obtained at recruitment.

Laboratory analysis

Fasting blood samples were collected from all patients on the same day as the clinical examination. CRP levels were measured using turbidimetry (Beckman Coulter, California, USA), and ESR was measured according to the Fahraeus Westergren method in a routine clinical laboratory. HLA-B27 was detected using flow cytometry kits (IOTest HLA-B27-FITC/HLA-B7-PE, Beckman Coulter - Immunotech SAS; Marseille, France) and BDTM HLA-B27 Kit (BD Bioscience; San Jose, CA)) according to the manufacturer's protocol.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 5.1. A Kolmogorov-Smirnov test of normality was performed for all variables. Categorical variables were compared between groups using Fisher's exact test. Data for continuous variables are presented as the median with interquartile range (IQR), and variables were compared using Mann-Whitney tests if not stated otherwise. P values below 0.05 with CI 95% were considered statistically significant for all statistical evaluations.

Results

Demographic data

A total of 246 patients who fulfilled ASAS classification criteria for axSpA were included in this study. Table 1 shows patients' demographic data. The entire group consisted of 106 patients with AS (43.1%) and 140 patients with nr-axSpA (56.9%). There was no gender predominance in the entire group (male-to-female ratio: 53.3% vs. 46.7%). However, most of the nr-axSpA patients were females compared to the AS patients ($p<0.001$). There were no significant differences in age, BMI or smoking history between AS and nr-axSpA patients.

Mean age at the diagnosis was 33.2 years, and the disease duration from first symptoms was 7.8 years for the entire axSpA group. The first clinical symptoms developed earlier in patients with AS compared to patients with nr-axSpA ($p=0.001$). AS patients were younger at the time of diagnosis than nr-axSpA patients ($p=0.023$).

Clinical parameters

Disease activity as determined by ASDAS-CRP was 2.2 in the entire axSpA group, and it was significantly higher in AS patients compared to nr-axSpA patients ($p=0.022$). The mean BASDAI was 2.6 in the entire axSpA group, but it did not significantly differ between AS and nr-axSpA subgroups. AS patients exhibited significantly worse spinal mobility compare to nr-axSpA patients. AS patients exhibited worse BASFI compared to nr-axSpA patients ($p=0.030$).

Peripheral arthritis and hip arthritis were present in 27.6% and 13.0% of all axSpA patients, respectively. Patients with nr-axSpA exhibited peripheral arthritis more frequently and hip arthritis less frequently compared to AS patients ($p=0.001$ and $p=0.022$, respectively). SJC and TJC were significantly higher in nr-axSpA patients compared to AS patients ($p=0.021$ and $p=0.015$, respectively). There were no significant differences in the first symptoms of the disease, extraarticular manifestations, or current and previous medications. Division of axSpA according to gender to compare joint variables (peripheral arthritis, hip arthritis, SJC and TJC) revealed a significant difference only in hip arthritis that was more frequent in male patients compared to female patients ($p<0.001$). Tables 1 and 2 present all clinical parameters.

Laboratory parameters

CRP serum levels ($p<0.001$) and ESR ($p=0.007$) were significantly higher in AS patients than nr-axSpA patients. HLA-B27 was found in most of the patients in this study (87.4%), and the prevalence of HLA-B27 was not significantly higher in AS patients than nr-axSpA patients. Tables 1 and 2 show all of the laboratory parameters.

Discussion

This study investigated similarities and differences between AS and nr-axSpA subgroups fulfilling the imaging arm of ASAS classification criteria in a single-centre axSpA cohort in Prague.

Demographic characteristics were comparable in both axSpA subgroups, except the male-to-female ratio, which was higher in AS patients than nr-axSpA patients, which is consistent with previous studies [8-11]. The nr-axSpA subgroup consisted of more female patients than the AS subgroup. Our data also demonstrated that nr-axSpA patients presented first symptoms of the disease later than AS patients, which is also consistent with some previous studies [20, 21]. Male gender and early onset of the disease in AS were proposed prognostic factors for severe radiographic damage [22, 23], and female gender was associated with milder disease and later onset [24]. Female predominance and later disease onset in nr-axSpA may underlie the lower percentage of nr-axSpA female patients progressing to AS [11].

Positive family history is a common finding in SpA. For example, siblings of HLA-B27-positive AS patients exhibit a 50 fold increased risk of developing AS compared to the general population [25]. Many patients, especially HLA-B27-positive patients, have a positive family history of SpA or related diseases. More than one third of all cases had first-degree relatives with AS, psoriasis or IBD in our study. Furthermore, recent findings even suggest that a substantial proportion of healthy first-degree relatives of HLA-B27-positive AS patients exhibit clinical and/or imaging abnormalities suggestive of SpA, and almost 33% may be classified as SpA especially as nr-axSpA [26]. Comparison of first degree relatives across gender did not reveal any differences, but a significantly greater frequency of positive family history was previously described in females [27, 28]. This result contrasts one study of the occurrence of SpA in first-degree relatives of patients in which no gender differences were demonstrated [29].

The disease activity of axSpA patients, using ASDAS score and CRP levels, differed between subgroups but remained similar when BASDAI was used in the present study. AS patients exhibited significantly higher disease activity as determined by ASDAS and acute phase reactants compared to nr-axSpA patients, which is consistent with previous studies [11, 30]. Elevated CRP may predict the development of radiographic changes [8]. However, recent findings demonstrated similar disease activity as determined by the BASDAI index between AS and nr-axSpA subgroups [8]. The BASDAI may not be a reliable index for evaluating disease activity in axSpA because it reflects subjective perceptions of the disease. Spinal

mobility measures and BASFI reflecting movement functions were significantly worse in the AS patients, which is consistent with the results of the GESPIC cohort [11]. These results are most likely due to advanced structural changes in the spine of AS patients.

A recent meta-analysis found that arthritis and extraarticular manifestations were equally prevalent in AS and nr-axSpA subgroups, except uveitis, which is slightly more prevalent in AS patients [12]. However, our study demonstrated a significant difference between the occurrence of peripheral arthritis, which was more frequent in the nr-axSpA than AS subgroup. A large SpA cohort recently demonstrated more peripheral involvement in females [27], which may explain the higher prevalence of peripheral arthritis in nr-axSpA with the larger female predominance, at least in the present study. Hip involvement was more frequent in AS patients than the nr-axSpA patients in our cohort. Hip involvement is more prevalent in patients with a younger disease onset, which may be associated with more severe axial disease, and it represents a prognostic factor for severe outcome [23, 31].

Our study has some limitations. First, four assessors examined the patients, which may cause possible inter-rater variability. Second, MRI was performed in several centres, and two MRI sequences were not available for re-assessment at the time of data analysis. Therefore, we followed the written report from the MRI examination to divide the patients into AS or nr-axSpA subgroups. We have tried to reduce possible bias by excluding patients fulfilling only the clinical arm of ASAS classification criteria and included only patients with sacroiliitis confirmed by MR (nr-axSpA) or conventional x-ray (AS). Patients fulfilling only the clinical arm had lower participation in the study and fulfilling only clinical arm of ASAS classification criteria provide relatively low sensitivity and specificity and sometimes causing questionable or borderline diagnosis.

Conclusions:

In summary, although disease activity, as determined by ASDAS and acute phase reactants, and functional limitations are worse in AS compared to nr-axSpA patients fulfilling the imaging arm of ASAS classification criteria, we confirmed that patients with nr-axSpA and patients with AS share some similar disease manifestations. However, they differ in gender ratio where woman are more prevalent in nr-axSpA than in AS subset and surprisingly, peripheral arthritis, unlike hip joint involvement, was more prevalent in nr-axSpA compared

to AS subset. To conclude, patients with nr-axSpA and AS exhibited many similarities despite the issue of classification, which suggests a common therapeutic approach.

List of abbreviations:

AS – Ankylosing spondylitis

ASAS - Assessment of SpondyloArthritis International Society

ASDAS - Ankylosing Spondylitis Disease Activity Score

AxSpA – Axial spondyloarthritis

BASDAI - Bath Ankylosing Spondylitis Disease Activity Index

BASFI - Bath Ankylosing Spondylitis Functional Index

BMI - Body mass index

BDMARDs - Biological treatment

CRP – C reactive protein

CsDMARDs - Conventional synthetic disease-modifying anti-rheumatic drugs

ESR – Erythrocyte sedimentation rate

IBD – Inflammatory bowel disease

MASES - Maastricht Ankylosing Spondylitis Enthesitis Score

MDGAS - Physician global assessment

MRI – Magnetic resonance imaging

MSASSS – Modified stoke axial spondyloarthritis spinal score

Nr-axSpA – Non-radiographic axial spondyloarthritis

NSAIDs - Non-steroidal anti-inflammatory drugs

PRASPAC - The Prague Spondyloarthritis Cohort

SD – Standard deviation

SJC – Swollen joint count

SI - Sacroiliitis

SpA - Spondyloarthritis

SPARCC - Spondyloarthritis Research Consortium of Canada

TJC – Tender joint count

Declaration

Ethic approval

The local ethics committee (Mgr. Ivana Půtova) of the Institute of Rheumatology in Prague approved this study. Written informed consent was obtained from all patients prior to study initiation.

The Patient and Public Involvement:

The patients and/or public were not involved in the design, recruitment or conduct of the study.

Conpeting of interest

All authors declare that they have no competing interests.

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Authors Contribution

MH, KB, LS, KP designed the study. MH, KB, SF, KZ, MG, JH, MF, MT, KP, JS prepared the clinical database or took clinical care of axSpA patients in the PRASPAC cohort. KB, MT, LS did the data analysis. KB, MT and LS drafted the manuscript. KB, JG determined the radiographic and MRI scores. All authors contributed to and approved the final manuscript.

Data sharing statement: No additional data are available. All data from the PRASPAC cohort are available to all qualified researchers/research groups on request.

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Tables:

Table 1 Baseline characteristics: demographic and clinical features of spondyloarthritis

Characteristic		SpA	nr-axSpA	AS	M-W/FET p
Age (years), median (IQR)		34.7 (29.3-43.5)	36.9 (29.2-46.9)	36.0 (29.3-44.1)	-
Gender:	Males number (%)	131 (53.3)	54 (38.6)	77 (72.6)	**< 0.001**
BMI (kg/m^2), median (IQR)		24.3 (21.7-27.4)	24.8 (21.6-28.2)	24.2 (22.6-26.6)	0.946
History of smoking:					
	Ever-smoker, number (%)	107 (43.7)	52 (37.1)	55 (52.4)	0.138
HLA-B27 positive, number (%)		215 (87.4)	117 (83.6)	98 (92.5)	0.051
Disease duration, years (IQR)		7.8 (3.1-14.5)	5.6 (2.6-12.2)	10.2 (5.1-15.5)	**0.001**
First symptom:					0.086
	Back pain, number (%)	195 (79.3)	104 (74.3)	91 (85.8)	
	Peripheral arthritis, number (%)	27 (11.0)	19 (13.6)	8 (7.5)	
	Extraarticular manifestations, number (%)	24 (9.8)	17 (12.1)	7 (6.6)	
Family history:					
	First degree relatives, number (%)	86 (35.0)	38 (27.1)	24 (22.6)	0.460
	Second degree relatives, number (%)	28 (11.4)	18 (12.9)	10 (9.4)	0.426
Past history of:					
	Peripheral arthritis, number %	68 (27.6)	50 (35.7)	18 (17)	**0.001**
	Hip arthritis, number %	32 (13.0)	12 (8.6)	20 (18.9)	**0.022**
	Uveitis, number %	63 (25.6)	39 (27.9)	24 (22.6)	0.379
	IBD, number %	13 (5.3)	9 (6.4)	4 (3.8)	-
	Psoriasis, number %	1 (0.4)	0 (0)	1 (0.9)	-
	Other, number %	3 (1.2)	1 (0.7)	2 (1.9)	-
Current symptoms:					
	MASES, median (IQR)	0.0 (0.0-2.0)	0.0 (0.0-2.0)	0.0 (0.0-1.3)	0.289
	SJC, mean (±SD)	0.4 (1.4)	0.5 (1.5)	0.3 (1.4)	**0.021**
	TJC, mead (±SD)	0.4 (1.4)	0.5 (1.4)	0.3 (1.7)	**0.015**
Current medication:					
	NSAIDs, number %	126 (51.2)	71 (50.7)	55 (51.9)	-
	CsDMARDs, number (%)	39 (15.9)	26 (18.6)	13 (12.3)	-
	Corticosteroids, number (%)	5 (2)	2 (1.4)	3 (2.8)	-
	BoDMARDs/bsDMARDs, number (%)*	6 (2.4)	2 (1.4)	4 (3.8)	-

AS, ankylosing spondylitis; BMI, body mass index; boDMARDs, biological original disease modifying anti-rheumatic drugs; bsDMARDs, biosimilar disease modifying anti-rheumatic drugs; csDMARDs, conventional synthetic disease modifying anti-rheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; IBD, inflammatory bowel disease; IQR, interquartile range; M-W/FETp, Mann-Whitney/ Fisher exact test p value; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; nr-axSpA, non-radiographic axial spondyloarthritis; SJC, swollen joint count; SpA, spondyloarthritis; TJC, tender joints count; *Adalimumab 2 patients; Certolizumab 1 patient; Golimumab 2 patients; Infliximab 1 patient

Table 2: Baseline characteristics: activity and metrology

Characteristic	SpA	nr-axSpA	AS	M-W/FET p
ASDAS-CRP, median (IQR)	2.2 (1.4-2.8)	2.0 (1.1-2.3)	2.4 (1.7-2.8)	**0.022**
BASDAI, median (IQR)	2.6 (1.2-4.7)	2.7 (1.0-4.9)	2.4 (1.2-3.7)	0.362
CRP mg/l	4.3 (1.2-12.0)	2.5 (0.8-8.2)	7.1 (2.6-14.9)	**< 0.001**
ESR mm/h	8.0 (4.0-17.8)	7.0 (3.0-16.0)	12.0 (4.4-22.0)	**0.007**
BASFI, median (IQR)	1.4 (0.5-2.1)	1.1 (0.3-2.9)	1.8 (0.7-3.3)	**0.030**
Metrology:				
Modified Schober (cm), median (IQR)	4.0 (3.0-5.0)	4.5 (3.5-5.5)	4.0 (3.0-5.0)	**< 0.001**
Occiput to wall (cm), median (IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	**< 0.001**
Chin-chest distance (cm), median (IQR)	1.5 (0.0-3.0)	1.0 (0.0-2.0)	2.0 (0.0-3.0)	**0.008**
Chest expansion (cm), median (IQR)	4.0 (3.0-6.0)	4.0 (3.0-6.0)	3.8 (2.0-6.0)	0.136

AS, ankylosing spondylitis; ASDAS-CRP - Ankylosing Spondylitis Disease Activity Score based on CRP; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; M-W/FETp, Mann-Whitney/ Fisher exact test p value; nr-axSpA, non-radiographic axial spondyloarthritis; SpA, spondyloarthritis

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Cross-sectional study of patients with Axial Spondyloarthritis fulfilling imaging arm of ASAS classification criteria: Baseline Clinical Characteristics and Subset Differences in a Single Centre Cohort

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Abstract

Objective: This study compared demographic, clinical and laboratory characteristics between patients with radiographic and non-radiographic axSpA.

Methods: In this single centre cross-sectional study a total of 246 patients with axSpA fulfilling the imaging arm of ASAS classification criteria were recruited. A total of 140 patients were diagnosed as nr-axSpA, and 106 patients had AS. Sociodemographic characteristics, disease manifestations, clinical and laboratory disease activity and their differences between subsets were analysed. P values below 0.05 with CI 95% were considered statistically significant.

Results: More nr-axSpA patients were females (61.4%) compared to 24.7% of AS patients. First symptoms developed earlier in AS patients compared to nr-axSpA (23.0 (IQR 17.5-30.0) vs. 27.8 (IQR 21.0-33.7) years, p=0.001). Disease manifestations did not differ, but patients with nr-axSpA experienced peripheral arthritis more frequently (35.7% vs. 17.0%, p=0.001) with less hip involvement (8.6% vs. 18.9%, p=0.022) compared to patients with AS. Patients with AS exhibited worse spinal mobility and physical function compared to nr-axSpA. Ankylosing Spondylitis Disease Activity Scores and CRP levels were significantly higher in patients with AS compared to nr-axSpA (2.4 (IQR 1.7-2.8) vs. 2.0 (IQR 1.1-2.3), p=0.022 and 7.1 (IQR 2.6-14.9) vs. 2.5 (IQR 0.8-8.2) mg/L, p<0.001, respectively).

Conclusions: Our data demonstrated some known and also novel differences between the two imaging arm fulfilling axSpA subgroups. Non-radiographic patients were mostly women who had experienced shorter disease duration, milder disease activity and better functional status with less hip involvement but more peripheral arthritis compared to patients with AS.

Strengths and limitations of this study:

- A strength of this study is the large sample size.

- This is the first study investigating the differences between axSpA patients in the Czech Republic.
- We included only patients fulfilling imaging arm of ASAS classification criteria (AS and nr-axSpA), patients fulfilling only clinical arm were not included.
- One of the limitations was that the MRI was performed in several imaging centres.

Key words: Spondyloarthritis, non-radiographic axial spondyloarthritis, ankylosing spondylitis, disease activity

Introduction:

Spondyloarthritis (SpA) is a frequent chronic inflammatory disease that primarily affects the axial skeleton and causes a typical lower back pain. SpA is a heterogeneous group of disorders that share common clinical features, including peripheral arthritis, enthesitis and extraarticular manifestations, such as uveitis, inflammatory bowel disease or psoriasis [1]. SpA is divided into predominantly axial or predominantly peripheral disease based on the sites of inflammation [2]. Ankylosing spondylitis (AS) is a prototype of axial spondyloarthritis (axSpA). The prevalence of axSpA is approximately 0.7-1.4% in the general population [3]. Patients generally develop signs of inflammatory back pain that correspond to sacroiliitis (or spondylitis) as detected by imaging. AS is a slowly progressive disease that is defined using modified New York classification criteria, in which conventional radiographs of the sacroiliac joints exhibit definite structural changes [4].

Many patients develop similar axial symptoms but lack the typical changes on radiographs, which potentially causes delayed or missed diagnosis [5]. Magnetic resonance imaging (MRI) is used to visualise the radiographic changes that typically occur several years after sacroiliac joint inflammation. MRI is also included in the new Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axSpA to enable the diagnosis of non-radiographic axSpA (nr-axSpA) [6]. Nr-axSpA may be a pre-stage of AS, however not all of these patients develop the destructive joint changes that are typical of long-standing disease. Only approximately 10-20% of patients with nr-axSpA develop structural changes and AS over in the subsequent two years, and approximately half of the patients exhibit radiographic sacroiliitis after five years of the disease [7].

Some recent studies investigated differences between these two subgroups [8-10]. These studies varied in male-to-female ratios, the proportion of patients with objective signs of inflammation (such as bone marrow oedema), and the proportion of patients with increased levels of C-reactive protein (CRP), all of which are higher in patients with AS [8-10]. Clinical characteristics such as disease activity, physical impairment and quality of life were comparable between these two subgroups [11, 12]. However, some inconsistencies exist. Therefore, our study described the baseline demographic, clinical, and laboratory characteristics of axSpA patients and examined differences between AS and nr-axSpA subgroups fulfilling the imaging arm of ASAS classification criteria.

Patients and methods

This study is a descriptive, single-centre, cross–sectional, ongoing study of the Prague Spondyloarthritis Cohort (PRASPAC), which included 246 patients who fulfilled the ASAS classification criteria for axSpA [13]. Patients with a suspicion of SpA were referred to our specialised early-SpA centre in the out-patient department of the Institute of Rheumatology mostly by general practitioners/ophthalmologists/rheumatologists (minority of patients by other specialists) from the central region of the Czech Republic. Patients were further classified as AS or nr-axSpA based on radiographic findings, and irrespective of the presence of psoriasis or inflammatory bowel disease (IBD). Patients were classified as nr-axSpA if radiographic changes in the sacroiliac (SI) joints of at least grade II bilaterally or grade III or IV unilaterally were lacking, and positive MRI (i.e., characteristic bone marrow oedema) was present with at least one SpA feature. Patients were classified as AS according to New York classification criteria [4]. Patients who fulfilled only clinical arm of ASAS classification criteria were included in the PRASPAC and underwent the same examination protocol. However, these patients were not included in our analyses. No restrictions for disease duration or treatment protocol were used at inclusion.

All patients were recruited from October 2012 to March 2016 at the outpatient rheumatology department of the Institute of Rheumatology in Prague and were followed every 6 months for the first 2 years. Trained rheumatologists obtained data related to the disease status according to recommended standardised methodologies: metrology (modified Schober, occiput to wall, chin-chest distance, chest expansion), Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) [14], swollen and tender joint count (SJC and TJC), physician global assessment (MDGAS), Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP) [15], Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [16], and Bath Ankylosing Spondylitis Functional Index (BASFI) [17]. Laboratory parameters (CRP and erythrocyte sedimentation rate [ESR]) were analysed from blood samples at each visit. Additional data related to the diagnosis were obtained at the recruitment visit, including age at the onset of first symptoms, type of first symptom (e.g., back pain, peripheral arthritis, extraarticular manifestations), age at diagnosis, family history (AS, IBD, psoriasis), inflammatory back pain, occurrence of peripheral or hip arthritis and extraarticular manifestations, previous and current medications (non-steroidal anti-inflammatory drugs [NSAIDs], conventional synthetic disease-modifying anti-rheumatic drugs [csDMARDs], glucocorticoids, biological treatment [bDMARDs]), HLA-B27 positivity and socio-demographic data (age, gender, body mass

index [BMI], current/ex/non-smoker). Both axSpA subsets were treated according to the EULAR recommendations for the management of spondyloarthritis. Patients with mild disease were treated with NSAIDs on demand. Most of the patients with previously developed peripheral arthritis were treated with csDMARDs. Patients with severe disease were treated with bDMARDs. The study was initiated before anti-TNF treatment was approved for nr-axSpA by local authorities. The local ethics committee of the Institute of Rheumatology in Prague approved this study. Written informed consent was obtained from all patients prior to study initiation. Data presented in this study were collected from the recruitment visit.

The Patient and Public Involvement:

The patients and/or public were not involved in the design, recruitment or conduct of the study.

Imaging

Radiographs of the SI joints and lumbar and cervical spine from all patients were obtained prior to recruitment, and a trained rheumatologist and/or central radiologist scored the radiographs for the initial disease classification. Radiographic sacroiliitis was scored from grade 0 (normal) to grade 4 (ankylosis) according to the Bennett scoring system [18]. Cervical and lumbar spines were scored according to the modified Stoke AS Spine Score (mSASSS) [19]. A trained rheumatologist scored MRI images from nr-axSpA patients obtained at recruitment.

Laboratory analysis

Fasting blood samples were collected from all patients on the same day as the clinical examination. CRP levels were measured using turbidimetry (Beckman Coulter, California, USA), and ESR was measured according to the Fahraeus Westergren method in a routine clinical laboratory. HLA-B27 was detected using flow cytometry kits (IOTest HLA-B27-FITC/HLA-B7-PE, Beckman Coulter - Immunotech SAS; Marseille, France) and BDTM HLA-B27 Kit (BD Bioscience; San Jose, CA)) according to the manufacturer's protocol.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 5.1. A Kolmogorov-Smirnov test of normality was performed for all variables. Categorical variables were compared between groups using Fisher's exact test. Data for continuous variables are presented as the median with interquartile range (IQR), and variables were compared using Mann-Whitney tests if not stated otherwise. P values below 0.05 with CI 95% were considered statistically significant for all statistical evaluations.

Results

Demographic data

A total of 246 patients who fulfilled ASAS classification criteria for axSpA were included in this study. Table 1 shows patients' demographic data. The entire group consisted of 106 patients with AS (43.1%) and 140 patients with nr-axSpA (56.9%). There was no gender predominance in the entire group (male-to-female ratio: 53.3% vs. 46.7%). However, most of the nr-axSpA patients were females compared to the AS patients ($p<0.001$). There were no significant differences in age, BMI or smoking history between AS and nr-axSpA patients.

Mean age at the diagnosis was 33.2 years, and the disease duration from first symptoms was 7.8 years for the entire axSpA group. The first clinical symptoms developed earlier in patients with AS compared to patients with nr-axSpA ($p=0.001$). AS patients were younger at the time of diagnosis than nr-axSpA patients ($p=0.023$).

Clinical parameters

Disease activity as determined by ASDAS-CRP was 2.2 in the entire axSpA group, and it was significantly higher in AS patients compared to nr-axSpA patients ($p=0.022$). The mean BASDAI was 2.6 in the entire axSpA group, but it did not significantly differ between AS and nr-axSpA subgroups. AS patients exhibited significantly worse spinal mobility compare to nr-axSpA patients. AS patients exhibited worse BASFI compared to nr-axSpA patients ($p=0.030$).

Peripheral arthritis and hip arthritis were present in 27.6% and 13.0% of all axSpA patients, respectively. Patients with nr-axSpA exhibited peripheral arthritis more frequently and hip arthritis less frequently compared to AS patients ($p=0.001$ and $p=0.022$, respectively). SJC and TJC were significantly higher in nr-axSpA patients compared to AS patients ($p=0.021$ and $p=0.015$, respectively). There were no significant differences in the first symptoms of the disease, extraarticular manifestations, or current and previous medications. Division of axSpA according to gender to compare joint variables (peripheral arthritis, hip arthritis, SJC and TJC) revealed a significant difference only in hip arthritis that was more frequent in male patients compared to female patients ($p<0.001$). Tables 1 and 2 present all clinical parameters.

Laboratory parameters

CRP serum levels ($p<0.001$) and ESR ($p=0.007$) were significantly higher in AS patients than nr-axSpA patients. HLA-B27 was found in most of the patients in this study (87.4%), and the prevalence of HLA-B27 was not significantly higher in AS patients than nr-axSpA patients. Tables 1 and 2 show all of the laboratory parameters.

Discussion

This study investigated similarities and differences between AS and nr-axSpA subgroups fulfilling the imaging arm of ASAS classification criteria in a single-centre axSpA cohort in Prague.

Demographic characteristics were comparable in both axSpA subgroups, except the male-to-female ratio, which was higher in AS patients than nr-axSpA patients, which is consistent with previous studies [8-11]. The nr-axSpA subgroup consisted of more female patients than the AS subgroup. Our data also demonstrated that nr-axSpA patients presented first symptoms of the disease later than AS patients, which is also consistent with some previous studies [20, 21]. Male gender and early onset of the disease in AS were proposed prognostic factors for severe radiographic damage [22, 23], and female gender was associated with milder disease and later onset [24]. Female predominance and later disease onset in nr-axSpA may underlie the lower percentage of nr-axSpA female patients progressing to AS [11].

Positive family history is a common finding in SpA. For example, siblings of HLA-B27-positive AS patients exhibit a 50 fold increased risk of developing AS compared to the general population [25]. Many patients, especially HLA-B27-positive patients, have a positive family history of SpA or related diseases. More than one third of all cases had first-degree relatives with AS, psoriasis or IBD in our study. Furthermore, recent findings even suggest that a substantial proportion of healthy first-degree relatives of HLA-B27-positive AS patients exhibit clinical and/or imaging abnormalities suggestive of SpA, and almost 33% may be classified as SpA especially as nr-axSpA [26]. Comparison of first degree relatives across gender did not reveal any differences, but a significantly greater frequency of positive family history was previously described in females [27, 28]. This result contrasts one study of the occurrence of SpA in first-degree relatives of patients in which no gender differences were demonstrated [29].

The disease activity of axSpA patients, using ASDAS score and CRP levels, differed between subgroups but remained similar when BASDAI was used in the present study. AS patients exhibited significantly higher disease activity as determined by ASDAS and acute phase reactants compared to nr-axSpA patients, which is consistent with previous studies [11, 30]. Elevated CRP may predict the development of radiographic changes [8]. However, recent findings demonstrated similar disease activity as determined by the BASDAI index between AS and nr-axSpA subgroups [8]. The BASDAI may not be a reliable index for evaluating disease activity in axSpA because it reflects subjective perceptions of the disease. Spinal

mobility measures and BASFI reflecting movement functions were significantly worse in the AS patients, which is consistent with the results of the GESPIC cohort [11]. These results are most likely due to advanced structural changes in the spine of AS patients.

A recent meta-analysis found that arthritis and extraarticular manifestations were equally prevalent in AS and nr-axSpA subgroups, except uveitis, which is slightly more prevalent in AS patients [12]. However, our study demonstrated a significant difference between the occurrence of peripheral arthritis, which was more frequent in the nr-axSpA than AS subgroup. A large SpA cohort recently demonstrated more peripheral involvement in females [27], which may explain the higher prevalence of peripheral arthritis in nr-axSpA with the larger female predominance, at least in the present study. Hip involvement was more frequent in AS patients than the nr-axSpA patients in our cohort. Hip involvement is more prevalent in patients with a younger disease onset, which may be associated with more severe axial disease, and it represents a prognostic factor for severe outcome [23, 31].

Our study has some limitations. First, four assessors examined the patients, which may cause possible inter-rater variability. Second, MRI was performed in several centres, and two MRI sequences were not available for re-assessment at the time of data analysis. Therefore, we followed the written report from the MRI examination to divide the patients into AS or nr-axSpA subgroups. We have tried to reduce possible bias by excluding patients fulfilling only the clinical arm of ASAS classification criteria and included only patients with sacroiliitis confirmed by MR (nr-axSpA) or conventional x-ray (AS). Patients fulfilling only the clinical arm had lower participation in the study and fulfilling only clinical arm of ASAS classification criteria provide relatively low sensitivity and specificity and sometimes causing questionable or borderline diagnosis.

Conclusions:

In summary, although disease activity, as determined by ASDAS and acute phase reactants, and functional limitations are worse in AS compared to nr-axSpA patients fulfilling the imaging arm of ASAS classification criteria, we confirmed that patients with nr-axSpA and patients with AS share some similar disease manifestations. However, they differ in gender ratio where woman are more prevalent in nr-axSpA than in AS subset and surprisingly, peripheral arthritis, unlike hip joint involvement, was more prevalent in nr-axSpA compared

to AS subset. To conclude, patients with nr-axSpA and AS exhibited many similarities despite the issue of classification, which suggests a common therapeutic approach.

List of abbreviations:

AS – Ankylosing spondylitis

ASAS - Assessment of SpondyloArthritis International Society

ASDAS - Ankylosing Spondylitis Disease Activity Score

AxSpA – Axial spondyloarthritis

BASDAI - Bath Ankylosing Spondylitis Disease Activity Index

BASFI - Bath Ankylosing Spondylitis Functional Index

BMI - Body mass index

BDMARDs - Biological treatment

CRP – C reactive protein

CsDMARDs - Conventional synthetic disease-modifying anti-rheumatic drugs

ESR – Erythrocyte sedimentation rate

IBD – Inflammatory bowel disease

MASES - Maastricht Ankylosing Spondylitis Enthesitis Score

MDGAS - Physician global assessment

MRI – Magnetic resonance imaging

MSASSS – Modified stoke axial spondyloarthritis spinal score

Nr-axSpA – Non-radiographic axial spondyloarthritis

NSAIDs - Non-steroidal anti-inflammatory drugs

PRASPAC - The Prague Spondyloarthritis Cohort

SD – Standard deviation

SJC – Swollen joint count

SI - Sacroiliitis

SpA - Spondyloarthritis

SPARCC - Spondyloarthritis Research Consortium of Canada

TJC – Tender joint count

Declaration

Ethic approval

The local ethics committee (Mgr. Ivana Půtova) of the Institute of Rheumatology in Prague approved this study. Written informed consent was obtained from all patients prior to study initiation.

Competing of interest

All authors declare that they have no competing interests.

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Authors Contribution

MH, KB, LS, KP designed the study. MH, KB, SF, KZ, MG, JH, MF, MT, KP, JS prepared the clinical database or took clinical care of axSpA patients in the PRASPAC cohort. KB, MT, LS did the data analysis. KB, MT and LS drafted the manuscript. KB, JG determined the radiographic and MRI scores. All authors contributed to and approved the final manuscript.

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Tables:

Table 1 Baseline characteristics: demographic and clinical features of spondyloarthritis

Characteristic	SpA	nr-axSpA	AS	M-W/FET p
Age (years), median (IQR)	34.7 (29.3-43.5)	36.9 (29.2-46.9)	36.0 (29.3-44.1)	-
Gender: Males number (%)	131 (53.3)	54 (38.6)	77 (72.6)	**< 0.001**
BMI (kg/m^2), median (IQR)	24.3 (21.7-27.4)	24.8 (21.6-28.2)	24.2 (22.6-26.6)	0.946
History of smoking:				
Ever-smoker, number (%)	107 (43.7)	52 (37.1)	55 (52.4)	0.138
HLA-B27 positive, number (%)	215 (87.4)	117 (83.6)	98 (92.5)	0.051
Disease duration, years (IQR)	7.8 (3.1-14.5)	5.6 (2.6-12.2)	10.2 (5.1-15.5)	**0.001**
First symptom:				0.086
Back pain, number (%)	195 (79.3)	104 (74.3)	91 (85.8)	
Peripheral arthritis, number (%)	27 (11.0)	19 (13.6)	8 (7.5)	
Extraarticular manifestations, number (%)	24 (9.8)	17 (12.1)	7 (6.6)	
Family history:				
First degree relatives, number (%)	86 (35.0)	38 (27.1)	24 (22.6)	0.460
Second degree relatives, number (%)	28 (11.4)	18 (12.9)	10 (9.4)	0.426
Past history of:				
Peripheral arthritis, number %	68 (27.6)	50 (35.7)	18 (17)	**0.001**
Hip arthritis, number %	32 (13.0)	12 (8.6)	20 (18.9)	**0.022**
Uveitis, number %	63 (25.6)	39 (27.9)	24 (22.6)	0.379
IBD, number %	13 (5.3)	9 (6.4)	4 (3.8)	-
Psoriasis, number %	1 (0.4)	0 (0)	1 (0.9)	-
Other, number %	3 (1.2)	1 (0.7)	2 (1.9)	-
Current symptoms:				
MASES, median (IQR)	0.0 (0.0-2.0)	0.0 (0.0-2.0)	0.0 (0.0-1.3)	0.289
SJC, mean (±SD)	0.4 (1.4)	0.5 (1.5)	0.3 (1.4)	**0.021**
TJC, mead (±SD)	0.4 (1.4)	0.5 (1.4)	0.3 (1.7)	**0.015**
Current medication:				
NSAIDs, number %	126 (51.2)	71 (50.7)	55 (51.9)	-
CsDMARDs, number (%)	39 (15.9)	26 (18.6)	13 (12.3)	-
Corticosteroids, number (%)	5 (2)	2 (1.4)	3 (2.8)	-
BoDMARDs/bsDMARDs, number (%)*	6 (2.4)	2 (1.4)	4 (3.8)	-

AS, ankylosing spondylitis; BMI, body mass index; boDMARDs, biological original disease modifying anti-rheumatic drugs; bsDMARDs, biosimilar disease modifying anti-rheumatic drugs; csDMARDs, conventional synthetic disease modifying anti-rheumatic drugs; NSAIDs, non-steroidal anti-inflammatory drugs; IBD, inflammatory bowel disease; IQR, interquartile range; M-W/FETp, Mann-Whitney/ Fisher exact test p value; MASES, Maastricht Ankylosing Spondylitis Enthesitis Score; nr-axSpA, non-radiographic axial spondyloarthritis; SJC, swollen joint count; SpA, spondyloarthritis; TJC, tender joints count; *Adalimumab 2 patients; Certolizumab 1 patient; Golimumab 2 patients; Infliximab 1 patient

Table 2: Baseline characteristics: activity and metrology

Characteristic	SpA	nr-axSpA	AS	M-W/FET p
ASDAS-CRP, median (IQR)	2.2 (1.4-2.8)	2.0 (1.1-2.3)	2.4 (1.7-2.8)	**0.022**
BASDAI, median (IQR)	2.6 (1.2-4.7)	2.7 (1.0-4.9)	2.4 (1.2-3.7)	0.362
CRP mg/l	4.3 (1.2-12.0)	2.5 (0.8-8.2)	7.1 (2.6-14.9)	**< 0.001**
ESR mm/h	8.0 (4.0-17.8)	7.0 (3.0-16.0)	12.0 (4.4-22.0)	**0.007**
BASFI, median (IQR)	1.4 (0.5-2.1)	1.1 (0.3-2.9)	1.8 (0.7-3.3)	**0.030**
Metrology:				
Modified Schober (cm), median (IQR)	4.0 (3.0-5.0)	4.5 (3.5-5.5)	4.0 (3.0-5.0)	**< 0.001**
Occiput to wall (cm), median (IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	**< 0.001**
Chin-chest distance (cm), median (IQR)	1.5 (0.0-3.0)	1.0 (0.0-2.0)	2.0 (0.0-3.0)	**0.008**
Chest expansion (cm), median (IQR)	4.0 (3.0-6.0)	4.0 (3.0-6.0)	3.8 (2.0-6.0)	0.136

AS, ankylosing spondylitis; ASDAS-CRP - Ankylosing Spondylitis Disease Activity Score based on CRP; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; M-W/FETp, Mann-Whitney/ Fisher exact test p value; nr-axSpA, non-radiographic axial spondyloarthritis; SpA, spondyloarthritis